

Claims

1. A transgenic non-human animal expressing at least one transgene comprising a DNA sequence encoding a heterologous Amyloid Precursor Protein (APP) comprising at least the Arctic mutation (E693G) and a further AD (Alzheimer's disease) pathogenic mutation or a further transgene affecting AD pathogenesis, which results in increased amounts of intracellular soluble A β aggregates, including A β peptides.
- 10 2. The transgenic animal according to claim 1, wherein the transgene/transgenes are integrated in the genomic DNA.
3. The transgenic animal according to claim 1 or 2, wherein said transgene/transgenes are operably linked to a promoter effective for expression of said gene in the brain tissue of said animal.
- 15 4. The transgenic animal according to any of claims 1-3 wherein the endogenous APP is expressive or non-expressive.
- 20 5. The transgenic animal according to any of claims 1-4, wherein said further transgene is a human presenilin-1 and/or presenilin-2 transgene harboring an AD pathogenic mutation.
- 25 6. The transgenic animal according to any of claims 1-4, wherein said further transgene comprises a DNA sequence encoding apolipoprotein E, apolipoprotein J (clusterin), α_1 -antichymotrypsin (ACT) or fragments thereof.
- 30 7. The transgenic animal according to any of claims 1-4, wherein said further AD pathogenic mutation is one of the APP mutations KM670/671DF, KM670/671DY, KM670/671EF or KM670/671EY.
- 35 8. The transgenic animal according to any of claims 1-4, wherein said further AD pathogenic mutation is one of the APP mutations KM670/671NL, KM670/671NY, KM670/671NF, KM670/671KL, KM670/671DL or KM670/671EL, wherein KM670/671NL (the Swedish mutation) is preferred.

9. The transgenic animal according to any of claims 1-4, wherein the transgenic animal expresses only one transgene which comprises only the Arctic mutation (E693G) and the Swedish mutation (KM670/671NL).
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10. The transgenic animal according to any of claims 1-9, additionally comprising a homologously integrated targeting construct for at least one of the neprilisin or insulin-degrading enzyme (IDE) genes, which disrupts these genes through gene ablation (knock-out) and enhances A β -40 and/or A β -42 Arctic peptide production.
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11. The transgenic animal according to any of claims 1-10 wherein the transgenic animal is a rodent.
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12. The transgenic animal according to any of claims 1-11 wherein the transgenic animal is a murine animal.
13. The transgenic animal according to claim 1-12, wherein the transgenic animal is a mouse.
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14. A method of producing the transgenic animal according to any of claims 1-13, comprising integrating in the genomic DNA at least one transgene comprising a DNA sequence encoding a heterologous Amyloid Precursor Protein (APP) comprising at least the Arctic mutation (E693G) and a further AD (Alzheimer's disease) pathogenic mutation or a further transgene affecting AD pathogenesis.
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15. The method according to claim 14, wherein said transgene/transgenes are operably linked to a promoter effective for expression of said gene in the brain tissue of said animal.
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16. The method according to any of claims 14-15 wherein the endogenous APP is optionally made non-expressive.

17. The method according to any of claims 14-16, wherein said further transgene is a human presenilin-1 and/or presenilin-2 transgene harboring an AD pathogenic mutation.
- 5 18. The method according to any of claims 14-16, wherein said further transgene comprises a DNA sequence encoding apolipoprotein E, apolipoprotein J (clusterin), α_1 -antichymotrypsin (ACT) or fragments thereof.
- 10 19. The method according to any of claims 14, wherein said further AD pathogenic mutation is one of the APP mutations KM670/671DF, KM670/671DY, KM670/671EF or KM670/671EY.
- 15 20. The method according to any of claims 14, wherein said further AD pathogenic mutation is one of the APP mutations KM670/671NL, KM670/671NY, KM670/671NF, KM670/671KL, KM670/671DL or KM670/671EL, wherein KM670/671NL (the Swedish mutation) is preferred.
- 20 21. The method according to any of claims 14-20, additionally comprising homologously integrating a targeting construct for at least one of the neprilysin or insulin-degrading enzyme (IDE) genes.
- 25 22. A method of screening, wherein the transgenic animal according to any of claims 1-13 is used for screening for agents useful for treating, preventing or inhibiting Alzheimer's disease.
23. A method of screening, wherein the transgenic animal according to any of claims 1-13 is used for screening for diagnostic agents for Alzheimer's disease.